Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 17, 25, 30-32, and 34-56 are pending in the application, with claim 17 being the independent claim. Claims 24, 27, 28, and 33 have been cancelled, while new claims 48-55 have been added. Support for claims 48, 49, and 50 can be found, *inter alia*, in cancelled claims 24, 27, and 28. Support for new claims 53 and 54 may be found, *inter alia*, at page 7, lines 7-13 of the specification. Support for new claims 55 and 56 may be found, *inter alia*, at page 4, line 25, through page 5, line 4 of the specification. Support for amendment to claim 17 may be found, *inter alia*, at page 3., lines 11-17, and at page 7,.lines 7-13 of the specification. Support for amendment to claim 32 may be found, *inter alia,* at page 6, lines 24-27, page 8, lines 18-26, and page 11, lines 16-19 of the specification. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph (enablement)

In the Final Office Action of May 23, 2003, the Examiner rejected claim 32 as allegedly non-enabled by the teachings in the specification. However, solely to advance prosecution and not in acquiescence of the Examiner's rejection, Applicants have

amended claim 32 to limit the adjuvant to a polycation and the peptide to a tumor antigen or a fragment thereof that is capable of binding to MHC molecules. Applicants respectfully traverse this ground of rejection as it may be applied to the pending claim.

In order for a claim to be enabled, the specification must teach one of ordinary skill in the art how to make and use the invention without undue experimentation. The factors that can be considered in determining whether an amount of experimentation is undue have been set forth in *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of experimentation involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, in *In re Angstadt*, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue:

> If to fulfill the requirements of 112, first paragraph, an applicant's disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

537 F.2d at 503, 190 U.S.P.Q. at 219 (emphasis in the original).

In making the rejection, the Examiner relied on an English language abstract of a Japanese language publication as support that claim 32 is not enabled. The Yamana *et al.* abstract reads:

> With the recent progress in molecular biology and gene technology, many new cancer-specific antigens have been identified. Many studies have demonstrated the role of HLA class I-restricted cytotoxic T lymphocytes (CTLs) in cancer specific-immunotherapies. We have also established HLA-A24- and A26-restricted and cancer specific CTLs from a patient with squamous cell carcinoma of the esophagus. Using CTLs, we identified a new gene SART-1 by cDNA-expression cloning and some SART-1-derived cancer rejection peptides were also identified. Further more, using the same approach, we identified a cyclophilin B gene that encodes antigenic epitopes recognized by the HLA-A24-restricted and tumor specific CTLs. Now we are performing phase I trials using these peptide vaccines and have found an increase in CTL precursor frequency in some cases in an in vitro study. However, other recent studies have reported that many tumors escape from CTL recognition by downregulation of HLA class I expression. Moreover, most cancer cells produce a suppressor agents [sic] against the immune system. Therefore, we must resolve these major problems to produce successful cancer vaccine therapy soon.

Yamana H. and Itoh, K., *Gan To Kagaku Ryoho* 27(10):1477-88 (2000).

The Examiner characterizes the teaching of Yamana *et al.* as follows:

> Yamana *et al* [sic] report of the identification of **several** possible tumor antigens. Yamana *et al.* further set forth that recent studies have reported that many tumors escape from CTL recognition by downregulation of HLA class I expression. In other words many tumor antigens have been identified, very few have proven to have any beneficial use.

Office Action at page 3 (emphasis in the original).

The Applicants respectfully disagree with the Examiner's characterization of the teachings of Yamana *et al.* Yamana *et al.* nowhere states that "many tumor antigens

have been identified, very few have proven to have any beneficial use." While Yamana *et al.* states that "[w]ith the recent progress in molecular biology and gene technology, many new cancer-specific antigens have been identified" and "other recent studies have reported that many tumors escape from CTL recognition by downregulation of HLA class I expression," Yamana *et al.* makes no necessary link between these two statements as the Examiner would have it. Because of problems inherent in ascertaining a teaching found in an abstract, in particular, an English language abstract of a foreign language publication, the Board of Patent Appeals and Interferences has deemed it inappropriate for an Examiner to rely on such documents to support a rejection[1].

Further, the Examiner has not provided any evidence or sound scientific reasoning why there is reason to doubt that one of ordinary skill in the art could, after reading the present specification, prepare *improved* vaccine compositions that have a greater efficacy towards tumor cells, even despite downregulation of HLA class I surface receptors. Applicants have surprisingly found that, a tumor vaccine substantially free from inorganic ions containing an MHC-binding peptide from a tumor antigen in combination with a polycation adjuvant and made isotonic has more potent anti-tumor activity than a conventionally formulated vaccine. The improved solubility and improved interaction of the peptide and adjuvant of such a vaccine result in increased uptake and presentation by the antigen presenting cells. The increased presentation by the antigen presenting cells to T-lymphocytes via MHC molecules results in greater T-lymphocyte activity against tumor cells.

---

1 In *Ex parte Jones*, the Board noted that "[a]bstracts often are not written by the author of the underlying document and may be erroneous. It is our opinion that a proper examination under 37 CFR § 1.104 should be based on the underlying documents and translations, where needed." *Ex parte Jones*, 62 USPQ2d 1206, 1208 (Bd. Pat. App. & Inter. 2001).

Based on the disclosure of the captioned application, one of ordinary skill in the art would appreciate that an innovative way to counter the *decreased* expression of HLA class I expression in tumor cells would be to *increase* the activity of the CTLs to which the HLA receptors bind. Yamana *et al.* is silent on the efficacy of vaccines that are capable of producing this effect.

Finally, Applicants set forth in the Example that nearly 70% of mice injected with an isotonic salt free vaccine containing an MHC-binding peptide and polycation adjuvant remained tumor free up to 10 weeks after injection with tumor cells compared with about 40% of mice injected with a conventionally formulated vaccine. These results strongly support that the instant claims are enabled.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 32 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for recitation of "derived from" because it is allegedly unclear if the antigens are undergoing any kind of chemical modification as implied by the term "derived from." Applicants respectfully traverse this rejection as it may be applied to the pending claim.

Solely to advance prosecution and not in acquiescence of the Examiner's rejection, Applicants have deleted "derived from" from claim 32 and have more particularly pointed out that the peptide can be a tumor antigen or a fragment thereof and that the peptide is capable of binding to MHC molecules.

In view of the above, Applicants believe that the claim satisfies the requirements of 35 U.S.C. § 112, second paragraph and respectfully request that the rejection be withdrawn.

Rejection Under 35 U.S.C. § 102(e)

The Examiner rejected claims 17, 24-25, 28-32, 35-36, 42, and 46-47 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,776,468 (the '468 Patent) to Hauser *et al.* Applicants respectfully traverse the rejection as it may be applied to the pending claims.

The Examiner attests that since no inorganic ions are recited in the claims of the '468 patent, "their presence is not a requirement, and therefore, the instant claims remain anticipated." The Examiner cited *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993), as supporting the proposition that limitations from the specification are not read into the claims.

However, solely to advance prosecution and not in acquiescence of the Examiner's rejection, Applicants have amended claim 17 to require that the adjuvant is a polycation. Hauser *et al.* does not disclose vaccine compositions that contain a polycation as the adjuvant.

Accordingly, Hauser *et al.* does not anticipate the instant claims. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections Under 35 U.S.C. § 103(a)

The Examiner rejected claims 17, 24-25, and 28-47 under 35 U.S.C. §103(a) as allegedly being unpatentable over Hauser *et al.* and Schmidt *et al.* in view of Chazono *et*

al. and McAleer *et al.* (U.S. Patent 4,338,335), Loudon *et al.* and McAleer *et al.* (U.S. Patent 4,147,772). Applicants respectfully traverse the rejection as it applies to the pending claims.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must show that the prior art suggested to those of ordinary skill that they should make the claimed composition or device, or carry out the claimed process, and that the invention could be attained with a reasonable expectation of success. See *In re Vaeck*, 20 USPQ2d (BNA) 1438, 1442 (Fed. Cir. 1991). Any suggestion and reasonable expectation of success must come from the prior art of record, not Applicants' disclosure. *Id.*

At the outset, Applicants believe that Loudon *et al.* is not prior art under 35 U.S.C. § 103 because the instant application's foreign priority date (January 30, 1998) is prior to the earliest U.S. filing date (April 29, 1998) of Loudon *et al.*

Further, Applicants contend that Hauser *et al.* is deficient because Hauser *et al.* does not teach peptide or protein vaccine compositions comprising polycation adjuvants substantially free from inorganic salt ions and made isotonic with either maltose, fructose, galactose, saccharose, sugar alcohols, lipids or combinations thereof. Schmidt *et al.* is silent on preparation of vaccines substantially free of inorganic salt ions and does not suggest the addition of maltose, fructose, galactose, saccharose, sugar alcohols, lipids or combinations thereof to make a vaccine isotonic.

The other documents the Examiner has relied on do not cure the deficiencies of Hauser *et al.* or Schmidt *et al.* The crux of the Examiner's argument is that each of Chazono *et al.*, McAleer *et al.* (U.S. Patent 4,338,335), Loudon *et al.*, and McAleer *et al.* (U.S. Patent 4,147,772) teach of the advantages of adding stabilizers to a vaccine

composition, in particular fructose, galactose, maltose, saccharose and mannitol, and therefore it would have been obvious to incorporate these stabilizers as well as the polyarginine adjuvant as taught by Schmidt *et al.* in a vaccine substantially free of inorganic salt ions. First, nowhere is it suggested in Chazono *et al.*, McAleer *et al.* (U.S. Patent 4,338,335), or McAleer *et al.* (U.S. Patent 4,147,772) that the aforementioned stabilizers be used in place of inorganic salts and are capable of making the solution isotonic or hypotonic as the instant claims require. On the contrary, each of Chazono *et al.*, McAleer *et al.* (U.S. Patent 4,338,335), and McAleer *et al.* (U.S. Patent 4,147,772) teach that these components are added to the vaccine to improve stability of the vaccine, e.g. to improve temperature resistance and storage shelf life. See column 4, lines 40-43 of Chazono *et al.*, Background of the Invention of McAleer *et al.* (U.S. Patent 4,338,335), and column 1, lines 13-17 and lines 57-59 of McAleer *et al.* (U.S. Patent No. 4,147,772). Moreover, the stabilizers described by Chazono *et al.*, McAleer *et al.* (U.S. Patent 4,338,335), and McAleer *et al.* (U.S. Patent 4,147,772) are present in combination with inorganic salts in the vaccine compositions. Thus, the documents teach away from using the stabilizers in the absence of inorganic salts.

Applicants have surprisingly found that, a vaccine substantially free from inorganic salt ions in combination with a polycation adjuvant and made isotonic is more immunogenic than a conventionally formulated vaccine. Nowhere in the documents cited by the Examiner is there a suggestion to formulate a vaccine such that it would have these improved properties. Therefore, there is no teaching or suggestion to make the claimed combinations as alleged by the Examiner.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Michele A. Cimbala (MICHELE A. CIMBALA)
Reg No. 33851
for Judith U. Kim
Attorney for Applicants
Registration No. 40,679

Date: June 21, 2004

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600